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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 09/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/700,270	GRIFFITHS, LYNETTE ROBYN	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 12-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 12-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11/13/00
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-7 and 12-16 and cancellation of claims 8-11 in the reply filed on August 1, 2005 is acknowledged. The preliminary amendment filed on 11/13/2000 is acknowledged and has been entered.

Priority

2. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in the instant application.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on November 2000 is acknowledged and has been considered by the examiner.

Claim Rejections - 35 USC § 112: Lack of Enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-7, 12-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The first paragraph of section 112 requires the specification describe how to make and use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any

necessary experimentation is "undue". These factors include but are not limited to: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented in the specification, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the unpredictability of the art and (8) the breadth of the claims. (See *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988)) *(MPEP 2164.01(a))*.

Enablement Issues

This enablement rejection is based on several fundamental enablement problems with the claims noted above. The first problem with the 1-4, 6-7, 12-16 is that theses claims are drawn to a method for diagnosing hypertension or Syndrome X or a predisposition to hypertension or Syndrome X which has a final process step which comprises "determining a risk polymorphism in the promoter of an inducible nitric oxide synthase (iNOS) gene. The specification does not, however, teach sufficient use for this determination. A diagnosis has a use, it is simply that there is no enablement for any particular diagnosis given the identification of any polymorphism or risk polymorphism in the iNOS gene. The problem with the claim 5 is that this claim is drawn to a method of prediction response to hypertension therapy by diagnosing genotype of the iNOS gene. The specification does not teach any use for this determination.

The nature of the invention

The claims are drawn to a method for diagnosing hypertension or Syndrome X or a predisposition to hypertension or Syndrome X by determining whether a risk polymorphism is present in the promoter of an inducible iNOS gene. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology". *Mycogen Plant Sci*, Inc, v, *Monsanto Co.* 243, F3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are dawn to any polymorphism capable of being present in the promoter of an iNOS gene. Likewise the claims are drawn to any genotype of an iNOS gene. Thus the claims can encompasses any polymorphism, including silent polymorphism in the promoter of an iNOS gene whether it be associated with a disease or condition, such as hypertension or Syndrome X or not. Additionally, the claims can encompass any genotype, disease-related or not, that can be found in the iNOS gene. Arguably, every polymorphism or genotype that may be found in a gene is not always associated with a disease or condition. Further, the polymorphism(s) or genotype(s) that may be present in the iNOS gene may not necessarily be associated with hypertension or Syndrome X. In fact, the art teaches the identification of risk polymorphism in the promoter of the iNOS gene that is associated with other diseases, such as atopy (see Konno et al, J. Allergy Clin. Immunol, Vol. 108, pages 810-814) and asymptomatic malaria-endemic populations (see Boutlis et al., Am. J. Trop Hyg. Vol. 60, No. 6, pages 569-573, 2003). The associations of theses risk polymorphisms in the promoter of the iNOS gene are associated with diseases with radically different etiologies, symptoms and with no relationship to each other or to hypertension or Syndrome X. The claims as broadly written encompass any possible mutation or polymorphism in the promoter of the iNOS gene and speculates that these polymorphism are associated with a risk of hypertension or Syndrome X, while the specification only identifies a single four base pair insertion located between position -891 and -575 5' to the translation start site in the promoter of the iNOS gene that may be associated with hypertension. The specification fails to provide any evidence of any polymorphisms in the iNOS gene that is associated with Syndrome X. Likewise, the specification further fails to define the sequence of

the four base pair insertion that is claimed to be associated with hypertension. Thus the claims encompass any four base pair insertion (4^4 sequences) located anywhere between positions -891 and -571 5' to the transcription start site in the promoter of the iNOS gene. Further, the claims encompass any genotype that may be present in the iNOS gene whether it be associated with a disease or condition or not. The specification fails to demonstrate any genotype that would be effective in defining a risk to the numerous diseases encompassed by the claims, including hypertension or Syndrome X. Hence, the specification is not fully commensurate in scope with the claims.

Quantity of Experimentation

The quantity of experimentation in this area is immense since there are numerous mutations and/or polymorphism that may be found in the promoter area of the iNOS gene that may be associated with a variety of different diseases. It would require significant study and experimentation including dozens of patients to determine that even a single disease is associated with any one of the different mutations and polymorphism in the iNOS gene that are broadly encompassed by claims. This would be an inventive, unpredictable and difficult undertaking in itself, and efficacy of any of the plethora of polymorphisms as diagnostic for any particular disease, need to be demonstrated in a variety of patients with a statistically significant result. This would require year of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Wacholder et al (J. Natl. Cancer Institute (2004), Vol. 96, no. 6, pages 434-442) notes with regards to association of mutations studies that larger studies with 1500 participates have significantly more statistical power than smaller studies (see page 435). So the quantity of

experimentation factor supports the conclusion that a large quantity of experimentation, with the use of may hundreds, perhaps even thousands, of patient samples would be necessary to demonstrate an association of a risk polymorphism located in the promoter region of an iNOS gene. To cover any fraction of the range of diseases that may be related to a polymorphism in the promoter region of the iNOS gene would involve tens of thousands of separate patients and the associated analyses would be required. Thus undue experimentation is left to one of skill in the art to practice the invention as claimed.

Working Examples and Guidance in the specification

The specification has no working examples of any of the many diseases which are associated either generically with a polymorphism or mutation in the promoter region of the iNOS gene or with any particular polymorphism or mutation sequence. While the specification has identified by name; not sequence, a four base pair insertion located between position -891 and -575 to the transcription start site in the promoter of the iNOS gene to be associated with hypertension, the specification provides no association of *any* risk polymorphism in the promoter region being associated with hypertension or Syndrome X or *any* diseases or condition being associated with a polymorphism in the claimed region of the iNOS gene. No correlation is made between a mutation or polymorphism anywhere in the iNOS gene and an association to Syndrome X. The specification provides no guidance on any specific diseases and any specific polymorphism besides a four base pair insertion that is claimed to be associated with hypertension. The specification provides no guidance on methods or techniques or demonstrated what the sequence of the four base pair insertion is that is claimed to be associated with hypertension and Syndrome X. In fact, the specification only appears to speculate that the

claimed method is effective in diagnosing Syndrome X without any substantial evidence. Due to the lack of working examples and guidance in the specification, undue experimentation is left to one of skill in the art to obtain the invention as claimed.

Unpredictability in the Art

The art teaches that it is unpredictable how a polymorphism in the promoter region of the iNOS gene is associated with any particular disease (see Boltlis et al., which teaches a polymorphism in the promoter region of the iNOS gene being associated with Malaria and Konno et al., which teaches wherein a polymorphism in the promoter region of the iNOS gene is associated with atopy). Moreso, it is unpredictable that every risk polymorphism found in the promoter of the iNOS gene will be associated with hypertension or Syndrome X. The absence of a specific relationship between a particular polymorphism and hypertension or Syndrome X or any specific disease is the central unpredictable element.

Thus, giving the unpredictability in the art, the lack of guidance and absence of working examples in the specification, the complex nature of the invention and the breadth of the claims which fails to recite more specifically which polymorphisms are specifically associated with which disease, the experimentation left to one of skill in the art is extensive and undue.

Claim Rejections - 35 USC § 112: Indefiniteness

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-6 and 12-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1-3, and 6 are indefinite because the claims lack a final process step that clearly relates back to the preamble. The claims are drawn to a method of diagnosing hypertension or a predisposition to hypertension. However, final step and only step recites, "determining whether a risk polymorphism is present in the promoter of an iNOS gene". Thus it cannot be determined if the goal of the preamble, i.e., for "diagnosing hypertension or a predisposition to hypertension" is achieved or not and if achieved, in what step it is achieved. Likewise, it cannot be clearly determined if the claims are intended to recited "a method of detecting a polymorphism in the iNOS gene". While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion (see *ex parte Erlich*, 3 UsPQ2d1011, p.1011 (Bd. Pat, Applicant. Int.1986). Clarification is required as to Applicant's intent.

(b) Claim 4 is confusing and indefinite because the claims are drawn to a method of diagnosing and treating hypertension by diagnosing hypertension or predisposition thereto according to claim 1, however the claim 1 does not recite method steps which diagnose hypertension or a predisposition thereto. Thus a clear nexus between the claim 1 and the claim 4 cannot be ascertained.

(c) Claim 5 is indefinite because the claims lack a final process step that clearly relates back to the preamble. The claims are drawn to a method of diagnosing hypertension or a predisposition to hypertension. However, final step and only step recites "diagnosing genotype of an iNOS gene". Thus it cannot be determined if the goal of the preamble, i.e., for

"diagnosing hypertension or a predisposition to hypertension" is achieved or not and if achieved, in what step it is achieved. Likewise, it cannot be clearly determined if the claims are intended to recited "a method of genotyping the iNOS gene". While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion (see *ex parte Erlich*, 3 UsPQ2d1011, p.1011 (Bd. Pat, Applicant. Int.1986). Clarification is required as to Applicant's intent.

(d) Claims 12-16 are indefinite because the claims lack a final process step that clearly relates back to the preamble. The claims are drawn to a method of diagnosing Syndrome X or a predisposition to Syndrome X. However, the final step and only step recites, "determining whether a risk polymorphism is present in the promoter of an iNOS gene". Thus it cannot be determined if the goal of the preamble, i.e., for "diagnosing Syndrome X or a predisposition to Syndrome X" is achieved or not and if achieved, in what step it is achieved. Likewise, it cannot be clearly determined if the claims are intended to recited "a method of detecting a polymorphism in the iNOS gene". While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion (see *ex parte Erlich*, 3 UsPQ2d1011, p.1011 (Bd. Pat, Applicant. Int.1986). Clarification is required as to Applicant's intent.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 1, 3, 5, 6, 12 and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by Xu et al (WO 97/38130, cited on IDS filed 11/2000). Regarding claims 1 and 12, Xu et al teach a method comprising determining whether a risk polymorphism is present in the promoter of an iNOS gene and association of the this polymorphism to numerous diseases (abstract and page 2, , 4, and Examples 1-7).

Regarding claim 3, Xu et al teach the method of claim 1, comprising determining whether an individual is homozygous or heterozygous for the risk polymorphism in the iNOS gene (page 3 and Examples 6 and 7).

Regarding claim 5, Xu et al teach a method comprising diagnosing genotype of an iNOS gene (page 4).

Regarding claims 6 and 14, Xu et al teach a method comprising screening the whole of a part of an iNOS gene for a polymorphisms in linkage disequilibrium with a polymorphisms in or near the promoter region of an iNOS gene (Example 6). Therefore, Xu et al meets the limitations of claims 1, 3, 5, 6, 12 and 14 of the instant invention.

9. Claims 1-2, 5 and 12-13 are rejected under 35 U.S.C. 102(a) as being anticipated by Bellamy et al (Clinical Genetics, Vol. 32, pages 192-193, September 1997). Regarding claim 11, 12, Bellamy et al teach a method comprising determining whether a risk polymorphism is present in the promoter of an iNOS gene (see page 192).

Regarding claims 2 and 13, Bellamy et al teach the method according to claim 1, wherein the risk polymorphism is a four base pair insertion located between position -891 and -575 to the

transcription start site in the promoter of the iNOS gene (see pages 192, especially Figure 1; Note* Bellamy does not expressly teach that the polymorphism is a four base pair insertion, however, the reference teaches the same promoter region of the iNOS gene amplified to detect the polymorphism of the instant invention. Bellamy further teaches the use of the same primers as depicted on page 7 (SEQ ID NOS: 2 and 3) of the specification to identify the polymorphic product; and finally, Bellamy identifies a product having the same size of the risk alleles (see figure 1) as that identified by Applicant based on genotyping (page 8 of specification)). Thus Bellamy et al meet the limitations of the instant invention.

Regarding claim 5, Bellamy et al teach a method of diagnosing genotype of an iNOS gene (see page 192 and Figure 1). Therefore, Bellamy meets this limitation.

Conclusion

10. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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CYNTHIA WILDER
PATENT EXAMINER
9/27/2005